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# Intra-cranial mechanisms for preserving brain blood flow in health and disease

Fiona D McBryde<sup>1,2</sup>, Simon C Malpas<sup>1</sup>, Julian FR Paton<sup>1,2</sup>

<sup>1</sup>Department of Physiology, Faculty of Medical and Health Sciences, University of Auckland, New Zealand

<sup>2</sup>School of Physiology, Pharmacology & Neuroscience, Biomedical Sciences, University of Bristol, Bristol, UK

## Abstract

The brain is an exceptionally energetically demanding organ with little metabolic reserve, and multiple systems operate to protect and preserve the brain blood supply. But how does the brain sense its own perfusion? In this review, we discuss how the brain may harness the cardiovascular system to counter threats to cerebral perfusion sensed via intracranial pressure (ICP), cerebral oxygenation and ischemia. Since the work of Cushing over 100 years ago, the existence of brain baroreceptors capable of eliciting increases in sympathetic outflow and blood pressure has been hypothesized. In the clinic, this response has generally been thought to occur only *in extremis*, to perfuse the severely ischemic brain as cerebral autoregulation fails. We review evidence that pressor responses may also occur with smaller, physiologically-relevant increases in ICP. The incoming brain oxygen supply is closely monitored by the carotid chemoreceptors, however, hypoxia and other markers of ischemia are also sensed intrinsically by astrocytes or other support cells within brain tissue itself, and elicit reactive hyperaemia. Recent studies suggest that astrocytic oxygen signalling within the brainstem may directly affect sympathetic nerve activity and blood pressure. We speculate that local cerebral oxygen tension is a major determinant of the mean level of arterial pressure, and discuss recent evidence that this may be the case. We conclude that intrinsic intra- and extra-cranial mechanisms sense and integrate information about hypoxia/ischemia and intracranial pressure, and play a major role in determining the long-term level of sympathetic outflow and arterial pressure, in order to optimise cerebral perfusion.

## ***Introduction***

The brain is a highly metabolically active organ, and despite only accounting for 2% of body weight, utilizes about 20% of total cardiac output and oxygen consumption to maintain normal function (Peterson et al., 2011, Clark and L., 1999). Unsurprisingly, there are numerous parallel, overlapping and interacting mechanisms and pathways by which the brain is protected from under-perfusion. In this paper we briefly review the ways in which cerebral perfusion may be sensed, and the pathways by which cardiovascular function may be modulated in order to protect and preserve the brain's blood supply. We also consider whether a reduction in cerebral perfusion could result in sustained increases in arterial pressure, and contribute to the development of hypertension.

## ***Cerebral Autoregulation of Cerebral Blood Flow***

Consistent with the concept that the maintenance of cerebral blood flow is of paramount importance, are the powerful auto-regulatory mechanisms present in the brain. These pathways have been thoroughly described in recent reviews (Tzeng and Ainslie, 2014, Willie et al., 2014), and therefore will be only briefly outlined here.

Cerebral autoregulation is underpinned by the intrinsic myogenicity of the cerebral vasculature, which permit changes in blood/perfusion pressure to be buffered, such that cerebral blood flow (CBF) remains constant. Current dogma holds that the degree of vasoconstriction is proportional to the change in perfusion pressure, such that flow is maintained at a constant level across a wide range of input pressures – generally accepted to be 50-160 mmHg (Lassen, 1959). Studies in anesthetized cats and rabbits have found that cerebral autoregulation continues to operate even after dual sympathetic and parasympathetic denervation, demonstrating that this response is not mediated by extrinsic innervation (Busija and Heistad, 1984). The mechanism(s) by which changes in incoming pressure and flow are sensed are not yet completely understood, but are thought to involve mechano-sensitive ion channels in the vascular smooth muscle of both small and large arterioles, which may respond to stretch and/or shear stress. The most likely mediators of myogenic depolarization are thought to be mechano-sensitive nonselective cation channels, such as TRPM4 (Reading and Brayden, 2007) and TRPC6 (Dietrich et al., 2005). In rats, inhibiting TRPC6 degradation has been shown to protect neurons after ischemic stroke (Du et al., 2010), a condition characterized by the loss of cerebral autoregulation in the region exposed to ischemia.

More recently, our understanding of the classic model of cerebral autoregulation has come under question. As pointed out by Tzeng *et al* (Tzeng and Ainslie, 2014) and others, Lassen's original autoregulation curve was based on measurements from *independent* subjects, many of whom had hyper- and hypo-tensive disorders. Thus, this curve with the classic extended 'autoregulatory plateau' does not necessarily reflect the pressure-flow relationship within an individual, as is often assumed. Furthermore, it has become clear that the experimental approaches taken to assess cerebral autoregulation may contain major confounds (Drummond, 1997, Tan, 2012, Tzeng et al., 2012, Tzeng and Ainslie, 2014, Willie et al., 2014, Numan et al., 2014). Specifically, to produce the required range of systemic arterial pressure in normal individuals generally requires the use of interventions (e.g. infusions of vasoactive drugs) that may themselves influence the cerebrovascular circulation (Stewart et al., 2013). Changes in systemic blood pressure can also be accompanied by

concurrent changes in arterial gases, which may invalidate indices of CBF such as transcranial Doppler (Smith et al., 2012, Tzeng et al., 2012, Willie et al., 2012). A recent meta-analysis pooling the within-subject responses in healthy individuals across 40 studies, suggests “a more pressure-passive relationship between MAP and CBF” than initially supposed (Numan et al., 2014). Within the pressure ranges studied (MAP levels 65-135% of baseline), there was little evidence of a plateau in CBF as blood pressure varied. Interestingly, Numan *et al* found evidence supporting autoregulatory hysteresis, with cerebral vasculature autoregulation more efficient at buffering increases in arterial pressure compared to falls (Numan et al., 2014), echoing similar findings in other studies (Aaslid et al., 2007, Schmidt et al., 2009). This finding has important implications for our understanding of cerebral perfusion - it may no longer be sufficient to accept that autoregulatory mechanisms alone can maintain CBF across a ‘physiological’ range of cerebral perfusion pressures, in particular when cerebral perfusion pressure falls.

### ***Metabolic Regulation***

Neurovascular coupling, or reactive hyperaemia, reflects the ability to modulate and redirect regional cerebral blood flow to meet local metabolic demand. The cerebral microvasculature is highly responsive to metabolite and chemical stimuli, in particular to carbon dioxide, pH and hypoxia (reviewed in (Paulson et al., 1990, Ainslie and Duffin, 2009, Fierstra et al., 2013)). The exact mechanism underlying this response is not fully clear, but the work of Nelson and colleagues has shown that modest increases in extracellular potassium ( $K^+$ ) can activate inward rectifier  $K^+$  channels in capillaries, which propagates back to intracerebral arteriole smooth muscle cells, causing hyperpolarization and vasodilation (Filosa et al., 2006, Dunn and Nelson, 2010). Further studies implicate astrocytes as key intermediaries linking neuronal activity to vascular smooth muscle (Filosa et al., 2004, Petzold and Murthy, 2011, Filosa et al., 2016). Blood flow at the microvascular level has been shown to increase very rapidly (<1s) after neuronal excitation, although the increase appears to be limited to within 250-500  $\mu$ m of the site of neuronal activity (Greenberg et al., 1979, Berwick et al., 2008). The cerebral vasculature is unique in that the large vessels play a major role in regulating blood flow, contributing around 50% of total cerebrovascular resistance at rest (Harper et al., 1984, Mayhan et al., 1986, Faraci and Heistad, 1990). This is in contrast to other organs, where the large arteries act primarily as conduit vessels, with resistance to flow provided by the arterioles and microvasculature (Zweifach and Lipowsky, 1984, Berne and Levy, 2010). Thus, while neurovascular coupling enables the redistribution of blood flow to active areas of the brain, the level of resistance in large arteries is a major determinant of microvascular perfusion pressure (Faraci and Heistad, 1990). Large vessel hemodynamic changes can be triggered by a number of factors, including intrinsic flow-mediated dilatation (Fujii et al., 1991), as well as systemic changes in blood gases sensed by peripheral chemoreceptors, which can trigger vasodilation across the cerebrovascular tree including the internal carotid and basilar arteries (Sato et al., 2012, Willie et al., 2012).

### ***Cerebral Autoregulation in Disease States***

While cerebral autoregulation and/or neurovascular coupling may be largely sufficient to protect cerebral perfusion in healthy individuals, this may not always be the case in some pathologies. In chronic hypertension, the cerebral autoregulatory curve has been shown to be right-shifted to buffer CBF around the elevated level of prevailing arterial pressure (Traon et al., 2002), and multimodal

imaging studies in rats have demonstrated that neurovascular coupling is impaired (Calcinaghi et al., 2013). Furthermore, there is strong evidence for impairments in both cerebral autoregulation and neurovascular coupling in the cerebral circulation of patients after ischemic stroke (Girouard and Iadecola, 2006, Aries et al., 2010). These impairments may leave the brain more vulnerable to cerebral hypoperfusion. Furthermore, it is unclear whether cerebral autoregulation/neurovascular coupling alone could compensate for sustained changes within the cranium, such as a global increase in intracranial pressure or chronic narrowing of the cerebral vasculature. We propose that in some cases it may be necessary to recruit an increase in systemic arterial pressure in order to maintain adequate cerebral perfusion. The intrinsic and extrinsic mechanisms which may trigger a neurally-mediated increase in arterial pressure will be discussed in some detail below.

### ***Intracranial pressure, arterial pressure and cerebral perfusion pressure***

Contained within a rigid cranium, the brain is uniquely vulnerable to changes in intracranial pressure (ICP), which if unopposed may result in compression of cerebral blood vessels or neural tissues, and present a barrier to brain blood flow. Cerebral perfusion pressure (CPP) is the difference between arterial pressure and ICP, and gives a measure of the “supply pressure” of blood to the brain, but does not necessarily predict cerebral blood flow. In health, resting intracranial pressure is low (5-10 mmHg) and largely determined by the balance between cerebro-spinal fluid production at the choroid plexus, ependyma and parenchyma, and drainage through absorption into cervical lymphatics or subarachnoid villi. At rest, with ICP low, CPP is largely determined by the level of arterial pressure. In pathological states such as cerebral haemorrhage, head trauma and hydrocephalus, ICP can increase profoundly, and uncontrolled intracranial hypertension can cause severe brain damage or death. ICP elevations unopposed by increases in arterial pressure can therefore reduce CPP; conversely, increases or decreases in arterial pressure can change CPP in the absence of changes in ICP. Additionally, prolonged exposure to malignant arterial hypertension can result in hypertensive encephalopathy through pressure-driven damage to the cerebral vasculature, oedema formation, and subsequent increases in ICP (Schwartz, 2002). Thus, the inter-relationship between ICP and arterial pressure is not always straightforward or well-understood, and will be discussed in detail below.

### ***The Cushing Response***

In 1901, Harvey Cushing first described a response, whereby substantial (50-100 mmHg) increases in intracranial pressure (ICP), via subdural saline infusions in anaesthetised dogs, were found to be balanced by matching elevations in arterial pressure (Cushing, 1901). Cushing proposed that the stimulus for this hypertensive response was brainstem ischemia or anoxia due to compression of cerebral vasculature by the raised intracranial pressure. Cushing’s response has since become known clinically as Cushing’s triad – a cluster of symptoms including irregular breathing and a vagally-mediated bradycardia, as well as severe arterial hypertension. Cushing’s Triad has been largely regarded as a last ditch effort to sustain cerebral perfusion in the face of near-terminal ischemic brain injury. This pressor response was later found to be abolished by sympathectomy, suggesting a critical role of the sympathetic nervous system (Hoff and Mitchell, 1972); a finding confirmed subsequently by measurement of plasma catecholamines (van Loon et al., 1993). Further studies have confirmed the occurrence of this Cushing’s response in various species (Rodbard and Stone,

1955, Thompson and Malina, 1959, Heyreh and Edwards, 1971, Fitch et al., 1977, Little and Oberg, 1981). An important consideration that arises from these earlier studies is that these experiments were all conducted under anaesthesia, and applied rather large increases in ICP (commonly 50-250 mmHg). This is not unreasonable, given the clinical setting in which Cushing's Triad generally occurs (pathological increases in ICP, in an unconscious patient), but extrapolation to a normal physiological ICP range remains problematic.

Experimental studies in conscious subjects have shown that arterial blood pressure is sensitive to much smaller changes in ICP than previously thought. Dickinson and McCubbin showed, in dogs, that the blood pressure response to raised cerebrospinal fluid pressure was more sensitive (20-30mmHg) with light or no anaesthesia (Dickinson and McCubbin, 1963). Nakamura *et al* performed intracerebroventricular infusions in conscious rats, using much smaller increments of intracranial pressure than Cushing's initial study, and found that changes in ICP as little as 1 mmHg were opposed by matching increases in arterial pressure (Nakamura et al., 1987). This finding has been further supported by studies in conscious human patients, which have examined the pressor effects of cerebrospinal (Dickinson and McCubbin, 1963) and intracerebroventricular infusions (Schmidt et al., 2005). These studies have led to the proposition that the response described by Cushing may in fact be a near-terminal exaggeration of a physiological mechanism involved in the day-to-day regulation of sympathetic drive and arterial pressure (Dickinson, 1990, Wan et al., 2008, Paton et al., 2009).

### **A "Brain Baroreceptor"?**

A key unanswered question is whether the resultant sympatho-excitatory pressor response represents a true "intracranial baroreflex", whereby changes in intracranial pressure are directly sensed; or whether increases in intracranial pressure are sensed via secondary changes in other variables such as reduced brain oxygen (hypoxia) or cerebral ischemia; a conundrum debated by Dickinson (Dickinson, 1990).

Experimental evidence suggests that certain sites within the brainstem seem to be especially sensitive to direct changes in pressure. In early studies in anesthetized dogs, Rodbard *et al* found that very large (200-250 mmHg) 'step' increases in ICP produced an immediate (<1s) increase in arterial pressure (Rodbard and Stone, 1955). The rapidity of this response was taken to indicate the presence of cerebral mechanoreceptors, as ischemia/anoxia were thought to take longer to develop; however the sensitivity of these putative mechanoreceptors to smaller ICP changes was not assessed (Rodbard and Stone, 1955). In anesthetized dogs, Thompson and Malina found that physically distorting the surface of the brainstem with a small metal rod without altering ICP produced increases in arterial pressure (Thompson and Malina, 1959). The location and sensitivity of mechano-sensitive areas was further refined by Reis and colleagues who, in a series of studies in anesthetized cats, identified a highly sensitive 'receptive area' beneath the floor of the 4<sup>th</sup> ventricle in the rostral ventrolateral medulla (RVLM), with a pressure threshold of around 8-20 mmHg (Hoff and Reis, 1970, Doba and Reis, 1972). Similarly, in anesthetized rats, Morimoto *et al* exposed the surface of the RVLM to pulsatile physical compression using a cannula tipped with a rubber membrane, and found that splanchnic sympathetic nerve activity and blood pressure increased with brainstem compression (Morimoto et al., 2000). Taken together, these results suggest that pressure-

sensitive mechanoreceptors present in the brainstem, with the ability to trigger a sympathetically-mediated increase in arterial pressure. However, these studies focussing on local tissue distortions do not determine whether this mechanism is able to respond to a generalized increase in ICP, where the elevations in cerebrospinal fluid pressure and interstitial pressure are likely to be balanced. The RVLM in particular has come under scrutiny as a possible “central baroreceptor”, potentially involved in setting the long-term level of sympathetic outflow and arterial pressure (Osborn, 2005, Geraldès et al., 2015). The cellular substrate(s) that may mediate such responses remain undetermined.

## **Physiological and Pathological Increases in ICP**

Below we consider a number of physiological and pathological situations in which ICP is known to be altered, and discuss what is known about arterial pressure regulation in these settings.

### *Head-down Tilt*

Head-down tilt is an example of a situation where intracranial pressure can be acutely and non-invasively increased in human subjects, and the cardiovascular responses recorded. Generally, there is a passive hydrostatic increase in both arterial and venous pressure to the head, which is accompanied by a transient baroreflex-mediated inhibition of systemic arterial pressure and sympathetic outflow (London et al., 1983). Interestingly, early studies show that almost 50% of hypertensive subjects show an absent or blunted response to head-down tilt compared to normotensive subjects, possibly due to changes in vascular compliance or baroreflex sensitivity (Green et al., 1956, London et al., 1983). More recently, head-down tilt was combined with transcranial Doppler, and found that head-down tilt was associated with a mild (3%) increase in middle cerebral artery blood velocity (Bosone et al., 2004). A major caveat is that head-down tilt also produces concomitant hydrostatic changes in arterial pressure at the level of the head, a shift in blood volume from the lower to the upper body, and a subsequent activation of both arterial and cardiopulmonary baroreflex pathways, which makes it difficult to identify the specific effect of ICP alone.

### *Cerebral Haemorrhage and Traumatic Brain Injury*

Profound systemic hypertension is a frequent feature of cerebrovascular events such as cerebral haemorrhage and head trauma (Rasool et al., 2004, Shiozaki, 2005). This increase in arterial pressure is usually associated with elevated ICP, due to direct bleeding into the parenchyma, ventricles or subarachnoid space, cerebral odema or hydrocephalus. Concurrent elevations in sympathetic drive have been demonstrated after both cerebral haemorrhage (Naredi et al., 2000) and traumatic brain injury (Clifton et al., 1981, Hinson and Sheth, 2012), and there is a positive association between hypertension severity and poor patient outcome (Willmot et al., 2004).

### *Hydrocephalus*

Although hypertension is itself a strong risk factor for developing adult-onset hydrocephalus (Krauss et al., 1996), few clinical studies on hydrocephalus have reported cardiovascular parameters. There is little clinical evidence to suggest a causative link between hydrocephalus and high blood pressure, although occasional case studies report the normalization of arterial hypertension following placement of a ventriculo-peritoneal shunt to relieve hydrocephalus (eg (Milhorat, 1971, Nunes et

al., 1994). Although hypertension can be a symptom of shunt malfunction in pediatric hydrocephalus, bradycardia has been found to have stronger prognostic value (Livingston et al., 2011). In the laboratory, intracisternal injections of the drug kaolin have been used to block CSF drainage and produce an experimental model of hydrocephalus, with ICP increased to roughly double baseline levels. Several early studies report sympathetically-mediated arterial hypertension following kaolin injections in dogs (Jeffers et al., 1937), rats (Griffith and Roberts, 1938) and rabbits (Edvinsson et al., 1971); although further studies do not support this observation (Foa et al., 1941), including one of our own utilizing continuous telemetric recordings of arterial pressure and ICP (Guild et al., 2015).

### ***The importance of the cerebral oxygen supply***

One possibility is that as well as, or instead of, intracranial pressure itself being sensed directly, the pressor response to raised ICP may occur in response to hypoperfusion or ischemia, as intracranial hypertension reduces cerebral perfusion pressure (McGillicuddy et al., 1978). An interesting extension of this idea is to consider whether a prolonged or persistent threat to cerebral perfusion might result in sustained systemic hypertension. The first clinical evidence supporting the link between cerebral perfusion and hypertension was described over 50 years ago by Dickinson and Thomson dissected out the femoral, internal carotid and vertebral arteries from 80 cadavers with varying degrees of essential hypertension, and the maximum flow-rate with perfusion at a fixed pressure was recorded for each vessel (Dickinson and Thomason, 1959, Dickinson and Thomson, 1960). Dickinson found that resistance in the cerebral vessels, and in particular the vertebral arteries, was closely correlated to ante-mortem blood pressure, with many vertebral vessels exhibiting narrowed lumens due to atherosclerosis or wall thickening. This relationship was considerably weaker in femoral arteries; contrary to the prevailing belief that hypertension was associated with a 'protective' generalized vasoconstriction across all vascular beds. This is an important finding, given that the large cerebral vessels contribute up to 50% of total cerebrovascular resistance (Harper et al., 1984, Mayhan et al., 1986, Faraci and Heistad, 1990). The critical question is whether these vascular changes are causally driving the development of hypertension in order to *preserve* brainstem perfusion, or whether these occur as a result of chronic exposure to the prevailing high arterial pressure, in order to *protect* the brainstem. Subsequent studies in the spontaneously hypertensive rat have revealed similar patterns of vertebral artery thickening, compared to normotensive controls, as shown in Figure 1 (Cates et al., 2011). Importantly, evidence for increased (~35%) vertebral resistance was found in pre-hypertensive rats as young as neonates, suggesting that congenital abnormalities in the brainstem blood supply pre-date, and may contribute to, the later rise in arterial pressure in this model (Cates et al., 2011, Cates et al., 2012a). Moreover, Figure 1 also shows that compression of vertebral arteries produced increases in sympathetic nerve activity and arterial pressure that were significantly greater in pre-hypertensive versus normotensive rats (Cates et al., 2011, Cates et al., 2012a). These and other studies have given rise to the "selfish brain" hypothesis of hypertension, which proposes that the brain puts the utmost priority on maintaining its own supply of blood and oxygen at the expense of systemic hypertension (Paton et al., 2009). (distinct from the 'selfish brain' hypothesis of metabolic abnormalities in neurological disorders (Mansur and Brietzke, 2012)). This concept is supported by observations in hypertensive human patients that total cerebral blood flow was reduced in essential hypertension



(Rodriguez et al., 1987), and more recently that elevated cerebrovascular resistance was both more common in hypertension, and positively related to sympathetic outflow (Hart et al., 2013, Hart et al., 2015). Interestingly however, our attempts to produce an experimental model of chronic brainstem hypoperfusion by ablating both vertebral arteries in Wistar rats only produced a transient hypertension, most likely due to the extensive and rapid remodelling of surrounding cerebral vessels to restore the blood supply (Baquero et al., 2012). If, as we propose, cerebral hypoperfusion may be a driving factor in essential hypertension, then it remains to be explored if compensation occurs or not, and if not then whether this causes hypertension in humans.

#### *(i) Extrinsic mechanisms*

A key set of organs monitoring the delivery of oxygen to the brain are the carotid bodies. Within the carotid body, there is extensive evidence that type I or glomus cells are the primary site of oxygen-sensing (reviewed in (Kumar and Prabhakar, 2012)). Exposing isolated glomus cells to even moderate hypoxia has been shown to trigger an increase in intracellular calcium, and dopamine release (Montoro et al., 1996), and to produce neural activity in co-cultured petrosal neurons (Zhong et al., 1997). Although the exact biochemical transduction mechanism is not fully known, recent evidence implicates a cascade involving the O<sub>2</sub>-dependant generation of carbon monoxide by the enzyme haeme oxidase; carbon monoxide in turn regulates the synthesis of the gaseous messenger hydrogen sulphide, which has been shown to directly influence ion-channel function, and hence depolarization (reviewed in (Prabhakar and Semenza, 2015)). Under normal physiological conditions, the carotid chemoreceptors exhibit low levels of firing (<1Hz), but have the ability to respond very robustly when stimulated, for example to a reduction in arterial pO<sub>2</sub> levels with altitude (Hansen and Sander, 2003) or apnoea (Dempsey et al., 2010). Stimulation of the peripheral chemoreceptor reflex invokes a powerful activation of the sympathetic nervous system, with concurrent increases in arterial pressure and respiration (Kara et al., 2003). Ablation or blockade of the carotid body has recently been identified as a promising potential treatment target for hypertension (Paton et al., 2013b, Paton et al., 2013a), producing substantial reductions in both sympathetic outflow and arterial pressure in spontaneously hypertensive rats (Abdala et al., 2012, McBryde et al., 2013). Interestingly, despite normal arterial pO<sub>2</sub>, tonic activity of the carotid chemoreceptors appears to drive increased sympathetic activity and arterial pressure in both the hypertensive rat (McBryde et al., 2013) and in human essential hypertension (Sinski et al., 2012, Sinski et al., 2014, Hart et al., 2016). We hypothesize that abnormalities in carotid body function may result in an inappropriate activation of sympatho-excitatory pressor pathways in the face of a “perceived” threat to cerebral perfusion, and thus driving chronic systemic hypertension. It remains to be determined whether carotid bodies directly control cerebral vascular resistance via autonomic neural pathways.

#### *(ii) Intrinsic mechanisms*

A key area of research has been to determine how an hypoxic or ischemic signal might be detected within brain tissue. A substantial emerging body of evidence supports the role of astrocytes as “neurovascular communicators”, sensing and responding to changes in neuronal activity or environment by regulating regional cerebrovascular tone (reviewed in (Filosa et al., 2016, Carmignoto and Gomez-Gonzalo, 2010)). Astrocytes have been shown to play a key intermediary role in the vasodilatory neurovascular coupling response, with increases in neuronal activity triggering activation of astrocytic calcium signalling pathways (Wang, 2006 #1482, Winship et al., 2007), and vasodilation (Mulligan and MacVicar, 2004, Gordon et al., 2008). Importantly when considering the potential relevance to normal physiology, astrocytes have been shown to respond rapidly to

decreases in  $pO_2$  as little as 2-3 mmHg below normal brain oxygenation levels, and drive ventilatory responses to systemic hypoxia in the absence of peripheral chemoreceptor input (Angelova et al., 2015). However, one wonders what the physiological function of this ventilatory response is when carotid bodies are intact and would provide the increase in ventilation. In our hands, removal of the carotid bodies produces a fall in respiratory rate in hypertensive animals which normalizes within 4-5 days, presumably due to central remodelling of respiratory control circuits (McBryde et al., 2013). Moreover, a ventilatory response to hypoxia was not seen in humans in whom bilateral carotid bodies were resected (Swanson et al., 1978, Niewinski et al., 2013).

A second possibility is that neurones themselves may directly sense and respond to an ischemic environment. Synaptic glutamate can trigger a neuronal influx of calcium via NMDA receptor, and thus activate neuronal nitric oxide synthase, increasing the production and release of the vasodilator nitric oxide (NO) (Busija et al., 2007). However, while the absence of NO appears to diminish neurovascular coupling (Ma et al., 1996), clamping NO concentrations at a steady level does not prevent the dynamic nature of the neurovascular coupling response (Lindauer et al., 1999); thus the role of NO may be permissive rather than direct.

A third possibility is that specific areas of the brain may act as oxygen-sensors to engage protective cardio-respiratory responses to low-oxygen threats. Because of its convenient anatomical placement and connections to cardiovascular/respiratory control centres, the brainstem region has come under close scrutiny. In the RVLM, pre-sympathetic neurones have been shown to be directly sensitive to hypoxia (Dampney and Moon, 1980, Sun and Reis, 1994, Koganezawa and Paton, 2014), while neurons in the nucleus tractus solitarii (NTS) are responsive to hypercapnia and pH (Dean et al., 1989, Nichols et al., 2008). This intrinsic sensitivity of RVLM presympathetic neurons to ischemia is demonstrated in Figure 2. In terms of signal transduction, haemoxygenase and the persistent sodium current have been described as playing key roles in RVLM neuronal sensitivity to hypoxia in vitro (Kangrga and Loewy, 1995, D'Agostino et al., 2009). As well as neurons, there is evidence that astrocytes within the brainstem may be critically involved in mediating the cardio-respiratory response to hypoxia, via ATP signalling pathways (Gourine et al., 2005, Erlichman et al., 2010). Recent work from our collaborators has shown that resting brainstem  $pO_2$  levels were lower in spontaneously hypertensive than normotensive rats (Marina et al., 2015). Furthermore, when arterial pressure was lowered to a normotensive level, brainstem tissue hypoxia was exacerbated (Marina et al., 2015). Further, the release of extracellular ATP and lactate with hypoxia mediate an increase in sensitivity to low  $pO_2$  in RVLM neurones, contributing to increases in sympathetic nerve activity and arterial pressure (Marina et al., 2015). Thus, the brainstem appears to be an important central site able to sense a low oxygen threat to the brain, modulate sympathetic outflow and raise arterial blood pressure in order to preserve cerebral perfusion.

### ***Ischemic stroke and the selfish brain***

It is important to note that the two general stimuli discussed above – physical (brainstem pressure/distortion) and chemical (cerebral hypoxia/ischemia) - are of course not mutually exclusive. If unopposed, intracranial hypertension will reduce cerebral perfusion pressure, which may result in ischemia and reduced brain tissue oxygen, if cerebral perfusion falls. Early studies in primates suggest that cerebral blood flow is not impaired until changes in ICP exceed 50 mmHg, although the

use of anesthetized subjects presents a potentially significant confound (Johnston et al., 1972, Rowan and Teasdale, 1977). It may thus be illuminating to consider a situation such as ischemic stroke, where both brain ischemia and moderate increases in ICP are known to occur.

Regardless of their prior blood pressure level, or the type of stroke suffered, the majority (80%) of patients show an abrupt and profound rise in blood pressure within 24 hours, often maintained for several weeks (Willmot et al., 2004, Qureshi, 2008). This increase in arterial pressure is accompanied by parallel increases in plasma noradrenaline (Myers et al., 1981, Sander et al., 2001). In many cases, intracranial hypertension may also occur, driven directly in haemorrhagic stroke (Naredi et al., 2000) or via cerebral oedema following ischemic stroke (Hacke et al., 1996, Willmot et al., 2004). The traditional view is that post-stroke hypertension functions to increase blood flow to salvageable tissue in the penumbra (Olsen, 1983, Semplicini et al., 2003), although others view post-stroke hypertension as a pathological response that should be prevented (Elewa et al., 2007, Fagan et al., 2006). This remains controversial and requires experimental evidence to resolve this clinically relevant question.

An interesting sub-set of stroke pathologies, are those which involve the posterior circulation supplying the brainstem. Cates *et al* found that infarction in the posterior circulation was more strongly associated with hypertension than infarcts in the anterior circulation (Cates et al., 2012b). These results are consistent with the brainstem being of particular importance as a central site for detecting and responding to hypoxia and ischemia, and evoking rises in arterial pressure.

We propose that post-stroke hypertension may be explained in terms of the selfish brain seeking to optimize cerebral perfusion at the expense of systemic hypertension. The question remains whether hypertension after stroke is occurring in response to the localised ischemia/hypoxia in the region of the infarct, or as a Cushing-like response to an oedema-driven increase in ICP, or to both. The former would suggest that either chemoreceptive “distress signals” are conveyed to the brainstem via the cerebral circulation, or alternatively that brainstem chemo-sensitive sites (e.g. RVLM) are not the only central locations with the ability to mediate a sympathetic activation in response to ischemia and/or decreased tissue oxygen. Furthermore, although the majority of patients exhibit post-stroke hypertension, many do not show increases in ICP, although ICP is not always assessed in the clinic. Our own work in conscious normotensive rats suggests that blood pressure increases abruptly and concurrently with the fall in brain tissue oxygen after experimental stroke, with a delayed, presumably oedema-driven, increase in intracranial pressure (McBryde, FD; unpublished observations, 2015). Thus, we predict that the key initiating factor driving post-stroke hypertension is likely to be ischemia/hypoxia, and that subsequent increases in ICP may further amplify and/or maintain the high blood pressure. These suggested pathways and interactions are summarized in Figure 3.

Interestingly, in traumatic brain injury, where around 15% of patients also show a transient hypertensive response for several days (Labi and Horn, 1990), it has been found that survival is more strongly predicted by brain tissue oxygen levels, than ICP or even cerebral perfusion pressure (Eriksson et al., 2012). This supports the notion that the brain may be more sensitive to perturbations in tissue oxygen, than absolute changes in pressure *per se*. One possibility is that a series of mechanisms with different thresholds operate together to maintain adequate cerebral oxygen levels via modulation of systemic arterial pressure.

## ***Conclusion and Perspectives***

We propose that some forms of neurogenic hypertension, and the hypertension associated with ischemic stroke may have a common origin. Our 'selfish brain' hypothesis proposes that intracranial mechanisms are present for preserving cerebral perfusion, but that this may be achieved at the expense of a sympathetically-mediated systemic hypertension. It remains unclear whether the intrinsic mechanisms that raise blood pressure in response to hypoxia/ischaemia and raised ICP occur in response to factors sensed throughout the brain, or solely in areas that control blood pressure through connections to the sympathetic nervous system. Transduction mechanisms are not fully resolved, but may include astrocytic–neuronal, as well as vascular–neuronal and vascular-astrocytic-neuronal signalling pathways, involving mediators such as ATP, lactate, nitric oxide, shear stress, and stretch-activated cation channels.

The implied clinical conundrum remains, as to whether lowering blood pressure in hypertensive patients with increased cerebrovascular resistance may be detrimental to brain perfusion and oxygenation, and thus increase risks for neurological conditions such as dementia (Ruitenberg et al., 2005). A similar problem is faced in stroke, where preventing the post-stroke surge in arterial pressure may risk compromising the patient's ability to perfuse damaged brain tissues (Oliveira-Filho et al., 2003). A lack of integrative physiological data in conscious subjects has made it difficult to resolve whether hypertension may be of physiological benefit in some situations, in terms of maintaining the brain blood supply. It is hoped that future basic science studies will be able to make use of new telemetry technologies (Guild et al., 2010, Russell et al., 2012, Guild et al., 2015), to open up the range of signals able to be assessed simultaneously (e.g. brain tissue PO<sub>2</sub>, arterial pressure and ICP) in the chronic, conscious setting to assess the positive and negatives of hypertension and brain blood flow.

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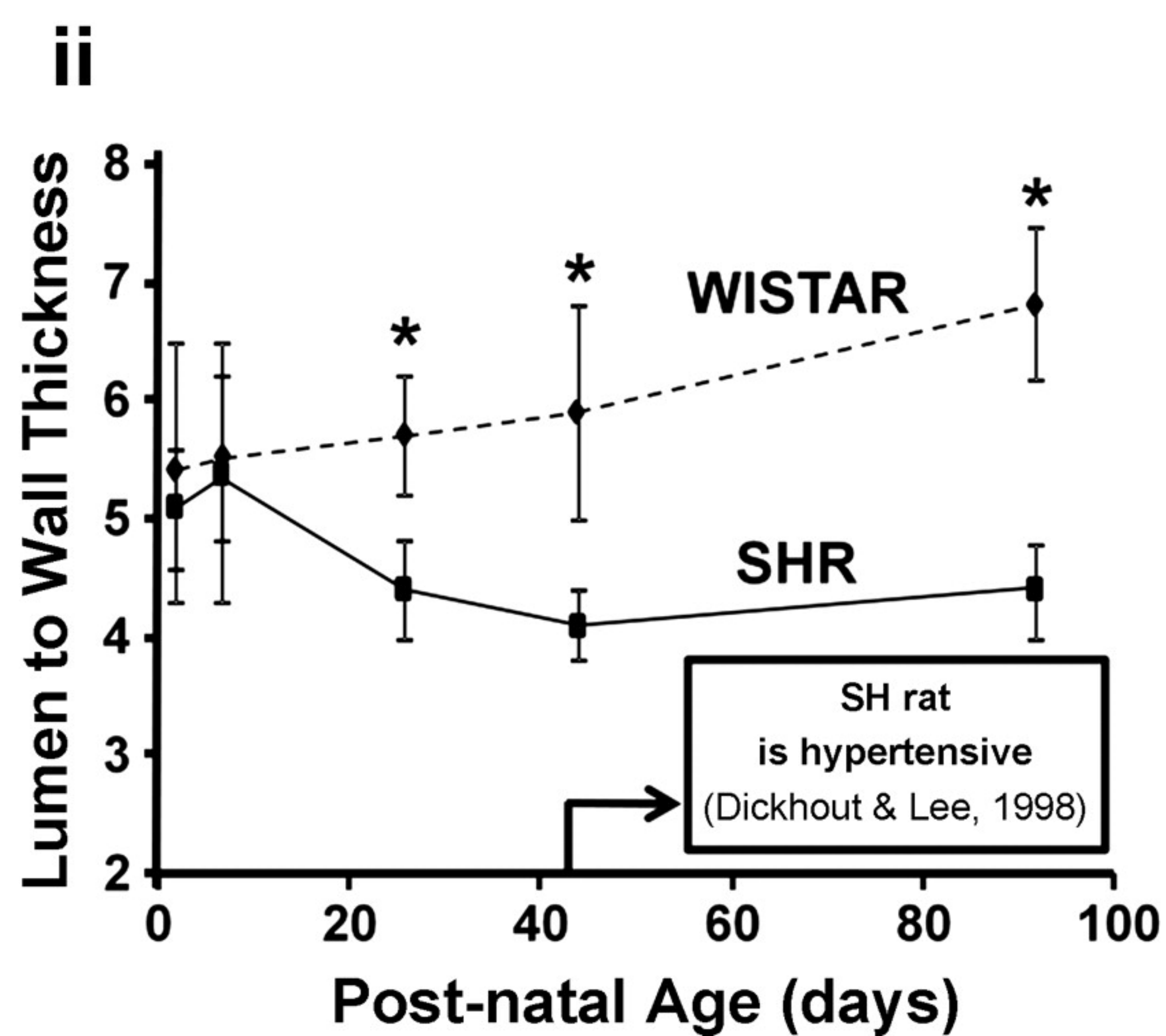
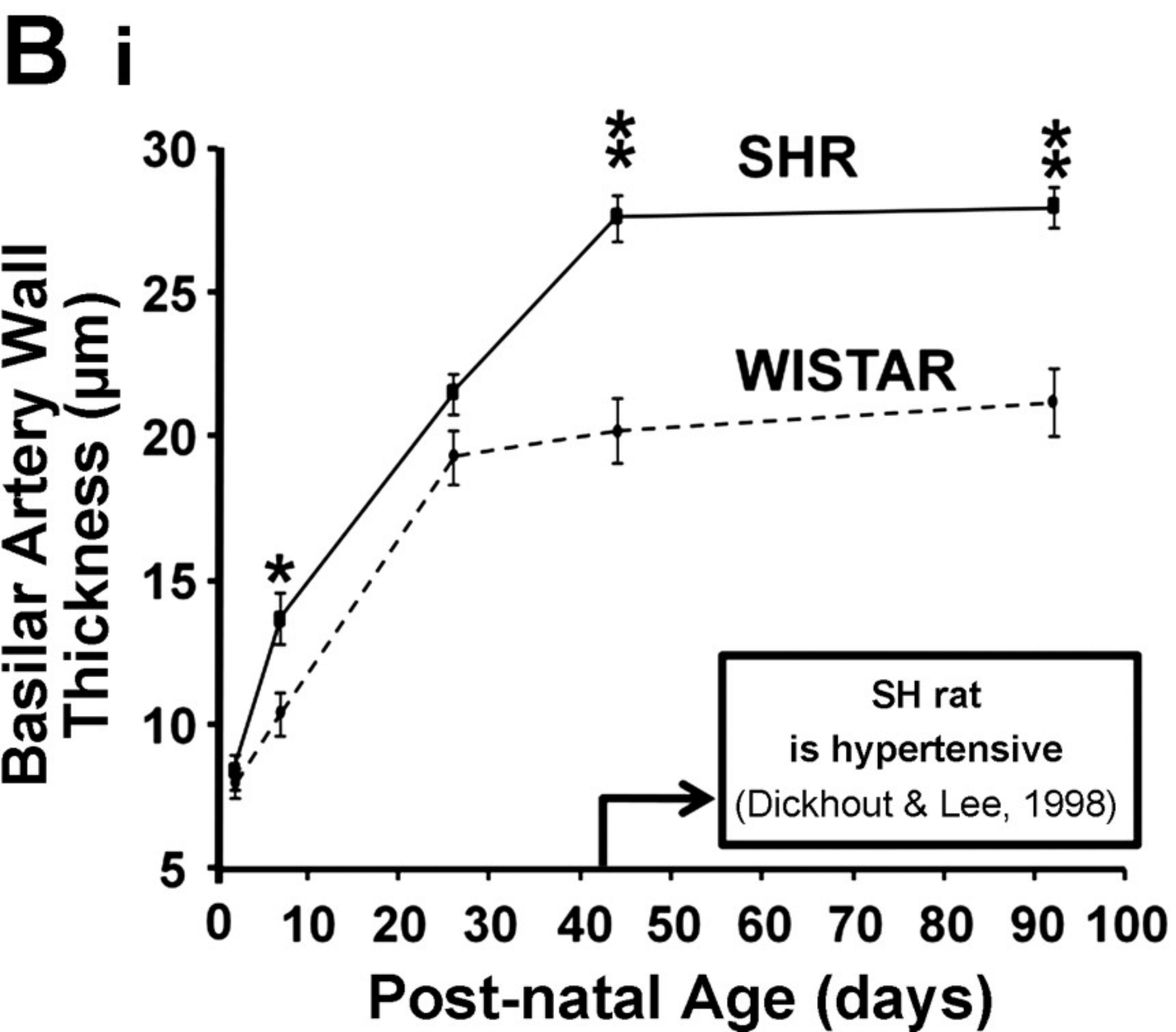
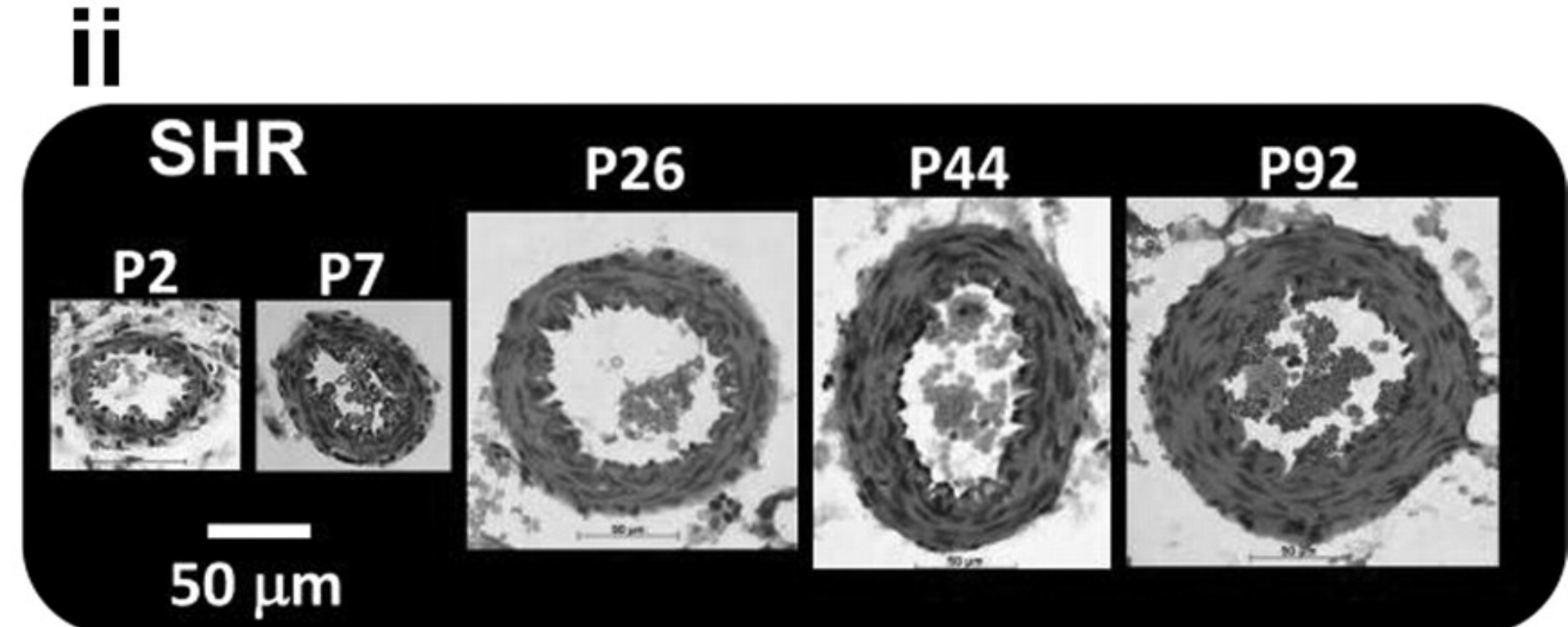
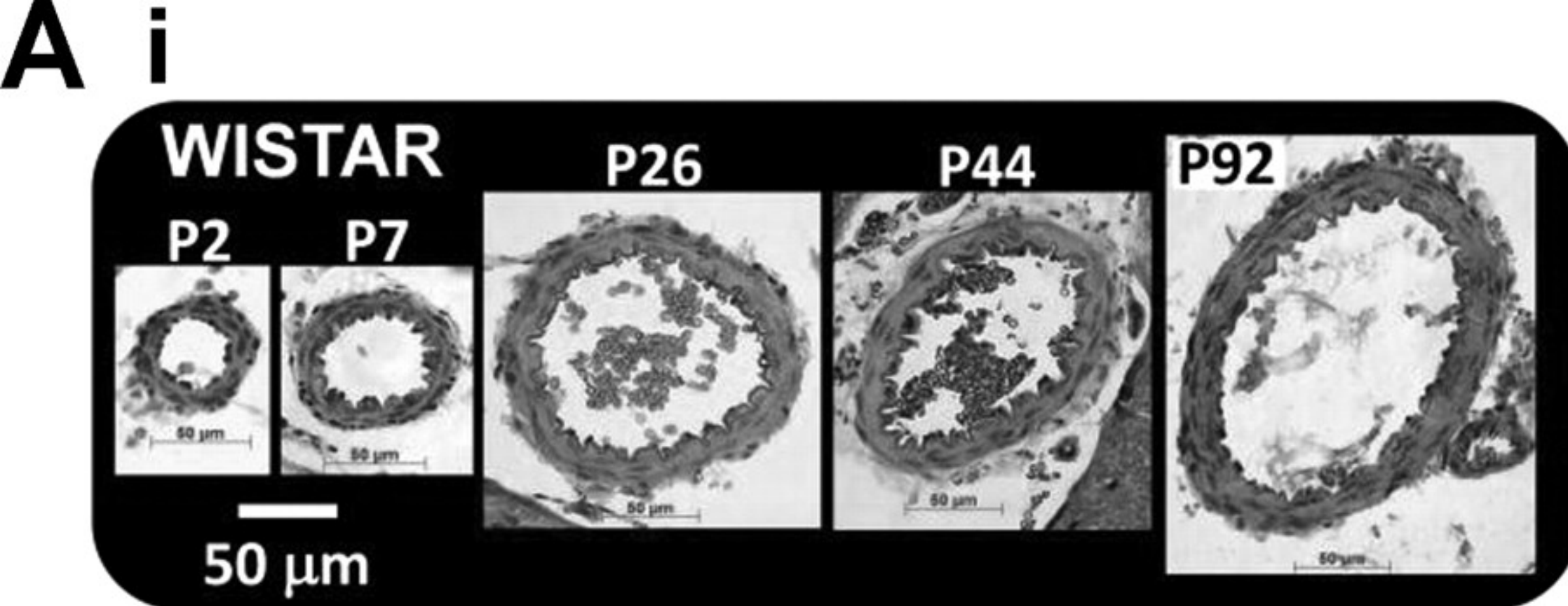
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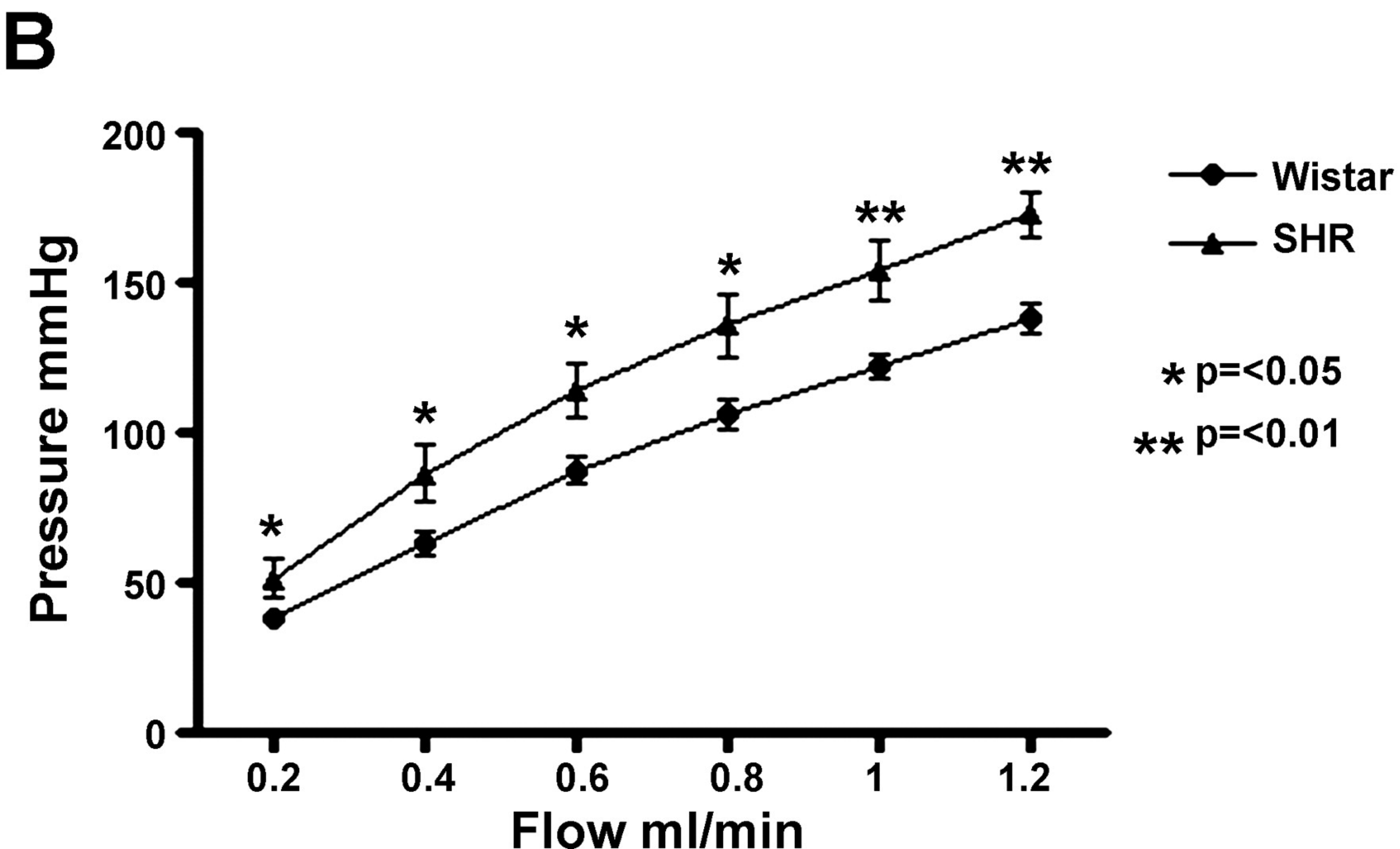
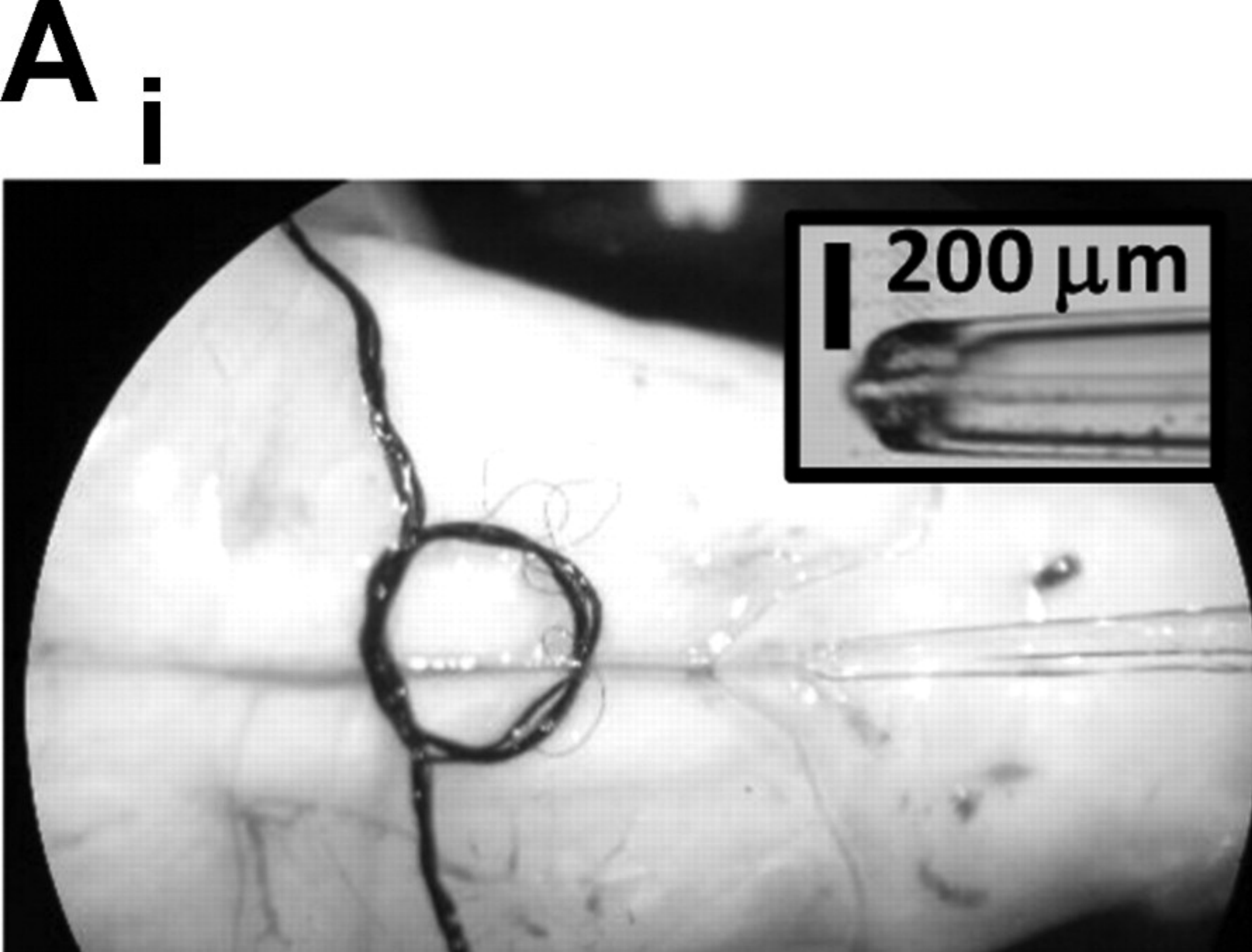
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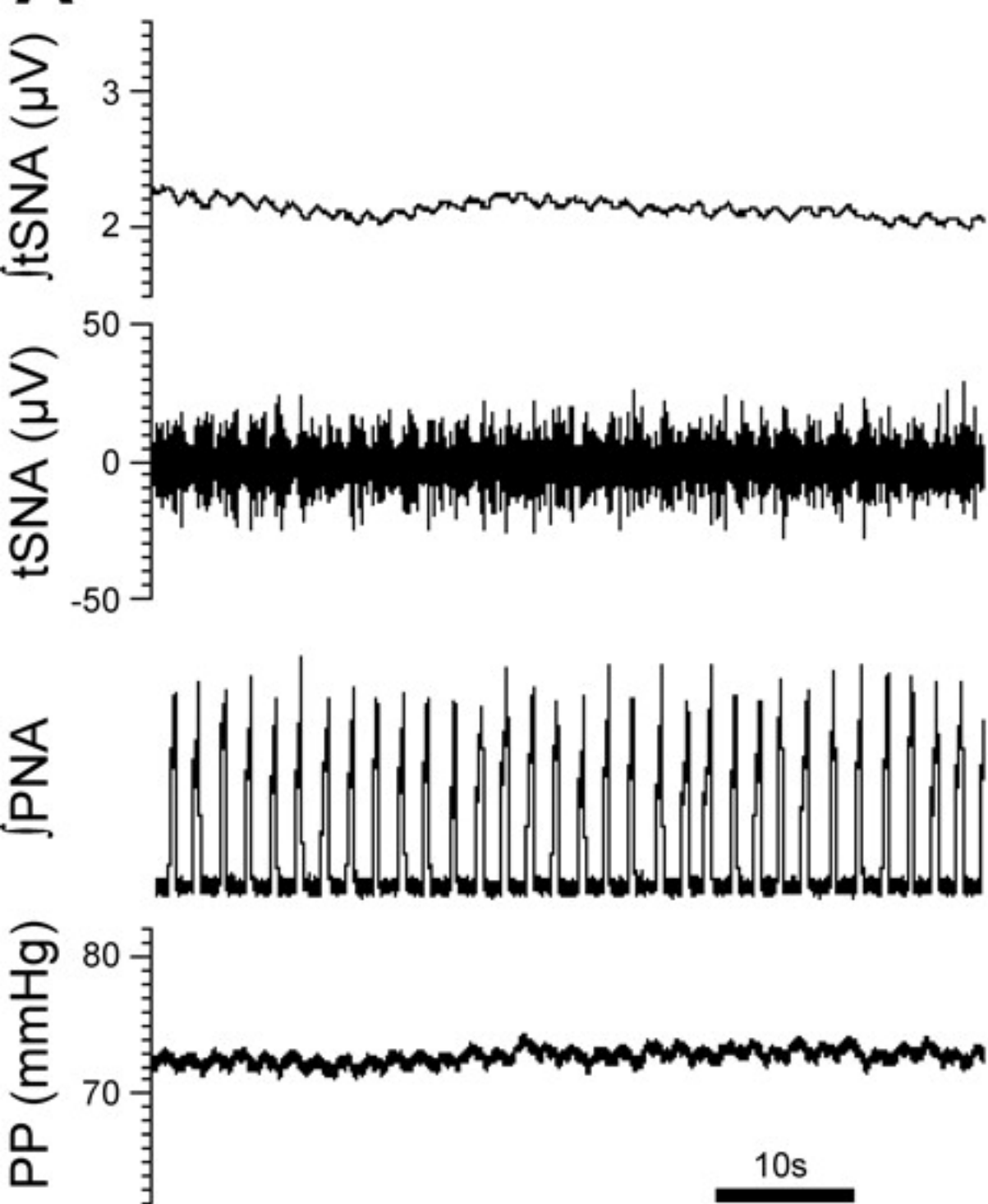
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**A**

LVA



Both VAs

**B**